Journal of Inflammation Research

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ORIGINAL RESEARCH

Predictors of Inadequate Serum Urate Response to Low-Dose Febuxostat in Male Patients with Gout

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Objective: This study aimed to understand predictors of inadequate response (IR) to low-dose febuxostat treatment based on clinical variables.

Methods: We pooled data from 340 patients of an observational cohort and two clinical trials who received febuxostat 20 mg/day for at least 3 months. IR was defined as failure to reach the target serum urate level (sUA<6 mg/dL) at any time point during 3 months treatment. The potential predictors associated with short- or mid-term febuxostat IR after pooling the three cohorts were explored using mixed-effect logistic analysis. Machine learning models were performed to evaluate the predictors for IR using the pooled data as the discovery set and validated in an external test set.

Results: Of the 340 patients, 68.9% and 51.8% were non-responders to low-dose febuxostat during short- and mid-term follow-up, respectively. Serum urate and triglyceride (TG) levels were significantly associated with febuxostat IR, but were also selected as significant features by LASSO analysis combined with age, BMI, and C-reactive protein (CRP). These five features in combination, using the best-performing stochastic gradient descent classifier, achieved an area under the receiver operating characteristic curve of 0.873 (95% CI [0.763, 0.942]) and 0.706 (95% CI [0.636, 0.727]) in the internal and external test sets, respectively, to predict febuxostat IR.

Conclusion: Response to low-dose febuxostat is associated with early sUA improvement in individual patients, as well as patient age, BMI, and levels of TG and CRP.

Keywords: gout, febuxostat, urate-lowering therapy, machine learning model

Introduction

Febuxostat is an effective urate-lowering therapy (ULT) agent.[1,2] Despite titration therapies following the treat-to-target strategy were widely adopted in the management of gout,[3–5] ~20-40% of patients do not achieve a target serum urate (sUA) level of <6 mg/dL taking febuxostat even at the highest daily dose.[6,7] In previous studies, some demographic or clinical variables emerged as predictive factors for serum urate inadequate response (IR) under ULT, such as low adherence, inadequate dosage, higher baseline sUA, and longer duration of gout[8,9] in clinical practice. However, the

Received: 17 February 2024
Accepted: 23 April 2024
Published: 30 April 2024

factors and underlying mechanisms specifically associated with the therapeutic response to febuxostat have not been well elucidated.

It was held that a "start low go slow" target strategy is recommended after initiating ULT,[2] as acute gout flares occur more often in the setting of a rapid and intensive reduction of the serum urate level.[10,11] However, such an approach embedded in the guidelines requires frequent monitoring of sUA and continuous supply of ULT.[12] To date, data on the optimal titration regimens are lacking. Exploratory clinical trials have recently described the efficacy of low-dose febuxostat over a mid-term period and reported that the rate of achieving the target (sUA < 6 mg/dL) was 32–45.7%.[13–15] A proportion of patients required a lower dose of febuxostat during early ULT. In contrast, continuous administration of low-dose febuxostat (10/20 mg/day) has been widely adopted after ULT initiation in clinical situations in Asia (*eg* China, Japan)[16,17] considering patient preferences and adherence. Dose adjustments of ULT medication occurred infrequently, with a mean time to any dose change of 211 days in the febuxostat group.[18] Taken together, identifying who will benefit from low-dose febuxostat has the potential to facilitate dose choice, while reducing frequent blood draws and patient visits. Patients treated with ULT need more optimal and tailored titration ULT regimens according to patient preferences, the timing of ambulatory encounters, and other factors in real-world management of gout.[2] Based on individual participant data from available trials, this study aimed to investigate the predictors associated with inadequate serum urate response to low-dose febuxostat during early ULT in pooled patients with gout.

Methods

Patients

We included participants from a prospective observational cohort in which gout patients were treated with 20 mg febuxostat and visited every 4 weeks to determine the predictive ability of CA-724 on gout flares (#ChiCTR2100043573)[19] and two RCT trials: a trial evaluating the efficacy and safety of chitosan oligosaccharide treatment (#ChiCTR2100042424), and a trial comparing the efficacy and safety of low-dose febuxostat and low-dose benzbromarone in gout patients (#ChiCTR1800019352). All participants took 20 mg of febuxostat without any dosage adjustments during 12 weeks. Overall, the inclusion criteria were: male patients with gout, age ≥ 18 years old, received at least 12 weeks of 20 mg febuxostat treatment, had available demographic, clinical, and follow-up data. Key exclusion criteria were estimated glomerular filtration<45 mL/min/1.73m^2, transaminases >2-fold of the upper normal limit, baseline sUA <7 mg/dL, and suffering from rheumatoid arthritis, or other serious diseases. Participants were defined as inadequate responders if they did not reach the target sUA (<6 mg/dL) at any time point during the short-term (4 weeks) or mid-term (12 weeks) follow-up. The study design is illustrated in Figure 1.

Variables

Demographic, clinical, biological, and radiological data (Table 1) were collected for each cohort at baseline. Tophi were assessed by clinical assessment. If the laboratories drawn varied between the discovery cohorts, only the common variables were reserved. Finally, 218 samples were selected as the discovery dataset with relatively complete 29 variables. To deal with missing data, k-nearest-neighbors-based imputation (KNN) was used on the discovery set when the missing value was <20%. In total, the 218 discovery samples were randomly divided into training and internal test sets (5:1 ratio). A variable selection process, least absolute shrinkage and selection operator (LASSO) regression according to the minimum criteria (lambda.min), was applied to all 29 available variables to select the most predictive features for the models, augmented with 10-fold cross-validation of the training dataset for internal validation. The R package 'glmnet' and 'impute' were used to implement the LASSO regression and the KNN imputation methods.

Models

Five machine-learning models were evaluated: logistic regression, random forest, stochastic gradient descent (SGD), extreme gradient boosting (XGBoost), and linear support vector classifier (SVC). The Python library Scikit-Learn was used to implement the machine learning models.

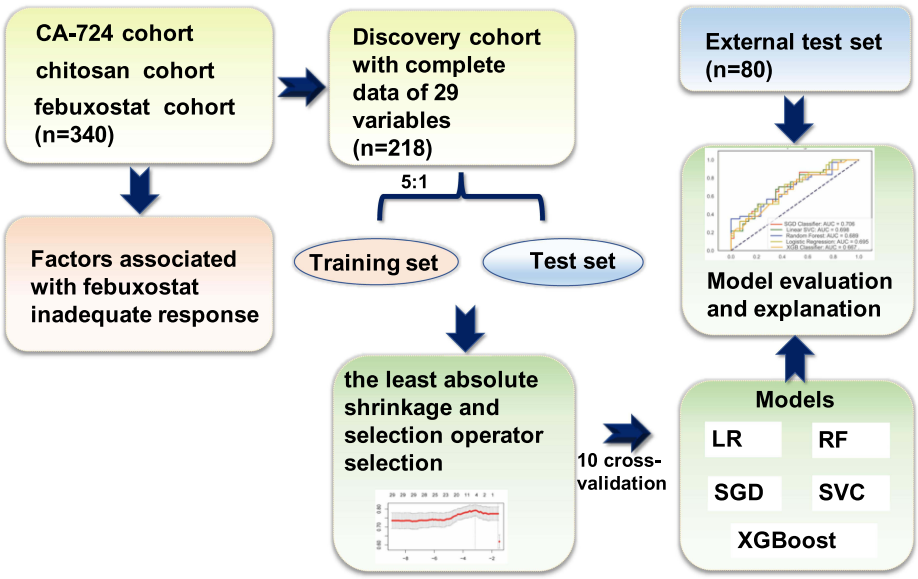

Figure 1 Study flow diagram. CA-724 cohort, cohort evaluating the predictive ability of CA-724 on gout flares (#ChiCTR2100043573); chitosan cohort, cohort evaluating the efficacy and safety of chitosan oligosaccharide treatment (#ChiCTR2100042424); febuxostat cohort, cohort comparing the efficacy and safety of low-dose febuxostat and low-dose benzbromarone in patients with gout (#ChiCTR1800019352).
Abbreviation: LR, logistic regression; RF, random forest; SGD, stochastic gradient descent classifier; SVC, support vector classifier; XGBoost, extreme gradient boosting.

First, cross-validation was performed during the modeling process to avoid overfitting and to allow for an unbiased model. An external test dataset from another trial (ChiCTR2000034138) was then used to evaluate the best-trained model output. The area under the receiver operating curve (AUC) was used to evaluate model performance. The positive and negative predictive values, sensitivity, and specificity were also computed, allowing model evaluation. Calibration of the prediction model was evaluated using calibration plots of observed and predicted risks and goodness-of-fit tests, with the number of boxes used to calculate quantiles set to 10. The larger the P value, the better the calibration of the prediction model. The R package 'rms' was used to plot calibration curves and calculate P-value statistics. To estimate the clinical utility of the prediction model, a decision curve analysis was employed using the R package "rmda" with the aim of calculating the net benefit of the threshold probability range in the training set and the test set. The threshold probability of decision curve analysis is that the expected return of the prediction is

Table 1 Characteristics of Participants in Each Cohort

	All	Discovery Cohort	External Test Cohort
	(N=340)	(N=218)	(N=80)
Age, years	45.9 (12.5)	46 (12)	49 (12)
BMI, kg/m^2	26.8 (3.3)	27.0 (3.4)	26.6 (2.9)
Systolic blood pressure, mmHg	134.6 (15.7)	134.6 (15.7)	136.1 (14.6)
Diastolic blood pressure, mmHg	87.3 (10.7)	87.3 (10.7)	87.6 (9.1)
Duration of gout, years	7.3 (6.2)	7.9 (6.3)	7.9 (6.7)
Family history, n (%)	75 (22.6)	47 (21.6)	21 (26.3)
Laboratory measures			
Serum urate, μmol/L	540.3 (71.3)	556.5 (74.8)	536.8 (66.4)
FBG, mmol/L	5.8 (0.7)	5.9 (0.7)	5.9 (0.7)
Triglyceride, mmol/L	2.0 (1.3)	2.1 (1.5)	2.1 (1.4)
Total cholesterol, mmol/L	5.0 (0.9)	5.0 (0.9)	5.3 (1.1)
ALT, U/L	27.5 (15.8)	27.6 (16.5)	28.2 (12.2)

(*Continued*)

Table 1 (Continued).

	All	Discovery Cohort	External Test Cohort
AST, U/L	22.6 (9.1)	22.9 (9.9)	21.6 (6.8)
Blood urea nitrogen, mmol/L	5.2 (1.4)	5.4 (1.5)	5.4 (1.2)
Serum creatinine, μmol/L	88.5 (16.6)	92.4 (17.6)	85.1 (10.2)
eGFR, mL/(min·1.73 m^2)	89.7 (18.5)	85.4 (17.7)	96.7 (14.3)
Ccr, mL/min	109.8 (30.5)	106.8 (30.5)	–
HDL-C, mmol/L	1.2 (0.3)	1.2 (0.3)	1.2 (0.2)
LDL-C, mmol/L	3.4 (0.9)	3.4 (0.9)	3.6 (1.0)
CRP, mg/L	2.8 (5.5)	2.8 (5.5)	3.9 (5.9)
ESR, mm/h	8.2 (7.3)	8.2 (7.3)	8.9 (7.7)
Ca72-4, U/mL	8.9 (42.7)	8.9 (42.7)	13.2 (56.8)
Lymphocytes, cells/10^9	2.3 (0.7)	2.3 (0.7)	-
Neutrophils, cells/10^9	3.9 (1.3)	3.9 (1.3)	-
White blood, cells/10^9	6.8 (1.8)	6.8 (1.8)	7.2 (1.6)
Clinical parameters			
Tophi, n (%)	147 (47.0)	138 (63.3)	39 (58.2)
Nephrolithiasis, n (%)	29 (13.1)	29 (13.3)	9 (14.5)
Bone erosion, n (%)	61 (28.6)	61 (28.0)	21 (33.3)
Double contour sign, n (%)	123 (58.0)	123 (56.4)	32 (50.8)
Synovial hypertrophy, n (%)	136 (64.5)	136 (62.4)	32 (50.8)

Notes: Data are shown as mean (standard derivation) or number (percentage).
Abbreviations: BMI, body mass index; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; Ccr, creatinine clearance rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

equal to the expected return to avoid the prediction. Decision curve analysis, a trade-off between false positives and false negatives, is primarily used to measure medical intervention strategies, screen beneficiaries, and evaluate the practical value of the entire model. To show the correlation between the model features, the correlation analysis between the features is visualized using the R package "circlize".

We performed SHAP (Shapley Additive exPlanations) on the training dataset to describe the weight of the given variables responsible for the model output. The SHAP value was used to quantify the proportion of positive and negative influences of the features on the prediction outcome for each patient, displaying an explanation diagram. The Python library SHAP and matplotlib were used for this analysis.

Statistical Analysis

For continuous variables, the *t*-test or Kruskal–Wallis test was performed as appropriate. Binary variables were compared between the two groups using the chi-squared test. A two-tailed p-value <0.05 was considered to indicate statistical significance. For all cohorts (340 patients), multilevel mixed-effect models were used to compute odds ratios (OR), with the study level as a random effect. Statistical analyses were performed using Stata Version 18.0.

Ethics Approval

The protocol of this study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. The scientific committees of the four cohorts approved the use of the data for this study.

Results

Study Cohorts

A total of 340 participants were pooled to investigate febuxostat responses. At week 4, 68.9% of the participants were non-responders, reporting sUA>6 mg/dL, and 51.8% were non-responders during the mid-term (12 week) follow-up. Of the 237 non-responders at short-term follow-up, 54 became responders during the mid-term follow-up period. Baseline characteristics of the patients with gout are summarized in Table 1.

Potential Factors Associated with IR

Age, BMI, sUA, TG, and Ccr during the 4-week follow-up period were significantly associated with febuxostat IR in the pooled population. With multivariate analysis, sUA was the only factor (OR 1.012, 95% CI 1.006–1.017). sUA and TG levels were both significant predictors during the mid-term follow-up (OR 1.017, 95% CI 1.012–1.023 and OR 1.439, 95% CI 1.061–1.951) (Table 2).

There was no difference in the febuxostat response during the short- or mid-term follow-up according to disease duration, combined with hypertension or nephrolithiasis, radiographic severity, or signs of inflammation (CRP and ESR) (Table 2).

Table 2 Factors Associated with Not Achieving the Serum Urate Target During Short- and Mid-Term Follow-Up

	Univariate			**Multivariate**
	n	**OR (95% CI)**	**p-value**	**OR (95% CI)**
Short-term				
Age	340	**0.970 (0.951–0.989)**	**0.002**	0.980 (0.945–1.017)
BMI	340	**1.115 (1.031–1.207)**	**0.007**	0.982 (0.852–1.131)
Duration of gout	319	0.989 (0.951–1.029)	0.577	1.034 (0.981–1.091)
Family history	332	0.708 (0.409–1.227)	0.218	0.575 (0.298–1.111)
Laboratory measures				
Serum urate	340	**1.012 (1.007–1.016)**	**<0.001**	**1.012 (1.006–1.017)**
Triglyceride	340	**1.654 (1.248–2.192)**	**<0.001**	1.295 (0.937–1.790)
Total cholesterol	340	1.147 (0.887–1.484)	0.295	0.979 (0.716–1.337)
FBG	340	1.089 (0.759–1.563)	0.642	1.323 (0.817–2.142)
Ccr	340	**1.015 (1.006–1.024)**	**0.001**	1.029 (0.999–1.060)
eGFR	340	1.005 (0.990–1.019)	0.527	0.971 (0.939–1.004)
CRP	227	1.068 (0.962–1.185)	0.218	
ESR	229	0.978 (0.940–1.018)	0.275	
Comorbidity				
Hypertension	331	1.189 (0.712–1.984)	0.508	1.177 (0.628–2.204)
Tophi	313	0.924 (0.510–1.673)	0.794	1.137 (0.626–2.066)
Nephrolithiasis	221	0.478 (0.208–1.100)	0.083	
Radiographic severity				
Synovial hypertrophy	211	0.849 (0.433–1.664)	0.633	
Bone erosion	213	1.435 (0.676–3.046)	0.347	
Double contour sign	212	0.918 (0.485–1.738)	0.793	
Mid-term				
Age	340	**0.979 (0.960–0.997)**	**0.024**	0.964 (0.928–1.002)
BMI	340	**1.139 (1.058–1.226)**	**0.001**	1.143 (0.985–1.326)
Duration of gout	319	1.003 (0.967–1.041)	0.873	1.049 (0.991–1.110)
Family history	332	0.857 (0.505–1.453)	0.566	0.501 (0.252–0.999)

(*Continued*)

Table 2 (Continued).

	Univariate			Multivariate
	n	OR (95% CI)	p-value	OR (95% CI)
Laboratory measures				
Serum urate	340	**1.015 (1.010–1.020)**	**<0.001**	**1.017 (1.012–1.023)**
Triglyceride	340	**1.724 (1.323–2.245)**	**<0.001**	**1.439 (1.061–1.951)**
Total cholesterol	340	1.147 (0.887–1.484)	0.152	1.012 (0.736–1.390)
FBG	340	1.158 (0.822–1.631)	0.402	1.360 (0.831–2.224)
Ccr	340	1.006 (0.998–1.013)	0.137	1.005 (0.976–1.036)
eGFR	340	0.990 (0.977–1.003)	0.146	0.978 (0.945–1.011)
CRP	227	**1.118 (1.007–1.242)**	**0.037**	
ESR	229	1.009 (0.972–1.048)	0.638	
Comorbidity				
Hypertension	331	1.364 (0.852–2.184)	0.195	1.188 (0.644–2.191)
Tophi	313	0.817 (0.476–1.403)	0.464	0.669 (0.360–1.244)
Nephrolithiasis	221	0.914 (0.410–2.038)	0.825	
Radiographic severity				
Synovial hypertrophy	211	0.878 (0.491–1.570)	0.660	
Bone erosion	213	0.698 (0.363–1.343)	0.282	
Double contour sign	212	0.916 (0.523–1.603)	0.757	

Notes: OR (95% CI): odds ratio (95% confidence interval). Bold text indicated significant. For the univariate analysis, a multilevel mixed-effects model was performed for each variable; for the multivariate analysis, only the variables with complete data (above 313) were used.
Abbreviations: BMI, body mass index; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; Ccr, creatinine clearance rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Variable Selection and Model Performance

In the discovery dataset, 218 patients receiving 20 mg of febuxostat daily for 12 weeks were included, of which 17% were selected as the internal validation set. A total of 138 patients out of 218 (63.3%) were identified as having febuxostat IR. Low-dose febuxostat inadequate responders were younger (43 vs 50 years, p<0.001) and had higher body mass index (BMI) (27.4 vs 26.4 kg/m^2, p=0.012), higher baseline sUA (585.4 vs 513.0 μmol/L, p<0.001), higher triglyceride (TG) (2.4 vs 1.6 mmol/L, p<0.001), lower high-density lipoprotein cholesterol (1.2 vs 1.3 mmol/L, p < 0.001), higher C-reactive protein (CRP) level (3.4 vs 1.8 mg/L, p=0.008), and a larger count of lymphocytes and white blood cells compared with those responders at baseline (Supplementary Table S1). Eighty patients were included in the external test dataset, with 37 (46.3%) identified as having febuxostat IR.

Five of the 29 variables available were selected as highly predictive combinations by LASSO: age, BMI, TG, sUA, and CRP levels (Figure 2A, B). Five machine learning models were then employed to predict the febuxostat therapeutic IR: random forest classifier, logistic regression, linear SVC, SGD Classifier and XGBoost. The performance of each model and their comparison with an external test dataset are shown in Figure 2C. The SGD Classifier performed best on the internal test dataset and achieved an AUC of 0.873 [95% CI: 0.763–0.942)]. The results replicated well in the external test set, with an AUC of 0.706 (95% CI [0.636, 0.727]) (Figure 3A).

The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the external test dataset are shown in Supplementary Table S2. Given that the SGD model had a higher AUC than the other models, it was further evaluated as the best model. The SGD model identified 70.3% (sensitivity, 95% CI: 65.9%, 88.2%) of inadequate responders in the test cohorts. The calibration curve of the SGD model was plotted in the testing set using five features (Figure 3B), with Hosmer-Lemeshow P=0.996. In addition, the decision curve results (Figure 3C) showed that the selected "age+sUA+BMI+CRP+TG" model exhibited a higher net benefit than the other models, as well as "All" (gray line) and "None" (black line). Patients would benefit more from the prediction of our model than from the no-prediction

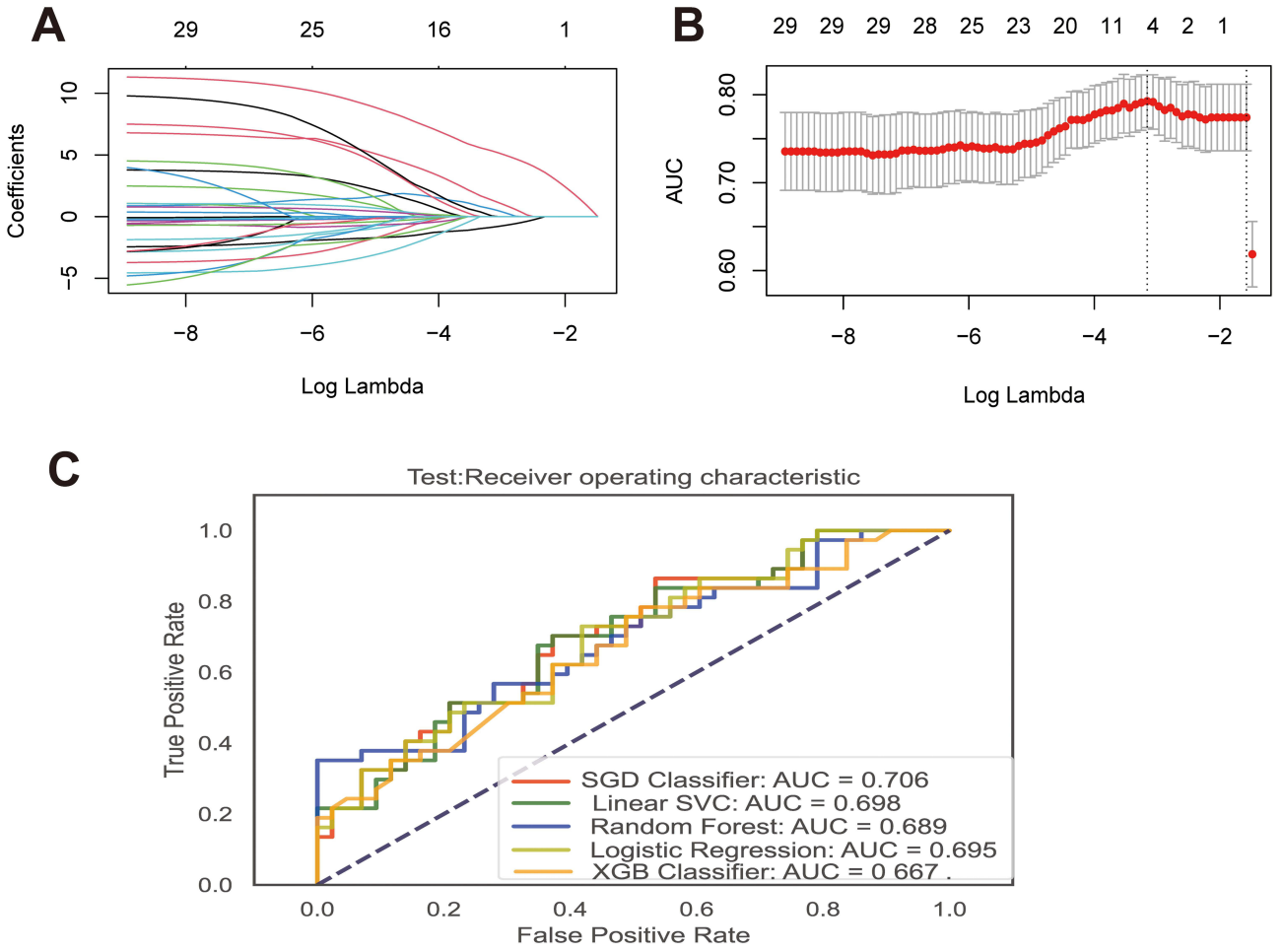

Figure 2 Variable selection and model performance. The area under the receiver operating characteristic curve (AUC) score of the 29 variables was determined using the LASSO model in the training set (**A**). Red dots represent the AUC score, gray lines represent the standard error, and vertical dotted lines represent the optimal values based on the minimum criteria. The upper abscissa is the number of nonzero coefficients in the model at this time, and the lower abscissa is log lambda, which is the tuning parameter used for the 10-fold cross-validation in the LASSO model. LASSO coefficient profiles of the 29 variables (**B**). The performance of each model and comparisons of the external test dataset (**C**). AUC: the area under the receiver operating characteristic curve.
Abbreviation: SGD, stochastic gradient descent classifier; SVC, support vector classifier; XGB classifier, extreme gradient boosting classifier.

schemes for most ranges. The correlation analysis between the features is shown in Figure 3D. Serum urate was positively correlated with TG (r=0.280) and negatively correlated with age (r=−0.217). These five features are not redundant to each other.

Explanation of Model

SHAP values were computed for the five variables selected by LASSO to investigate their impact on the IR prediction model. The magnitude of the importance was similar for the training/test and external test sets. When displaying the importance of the variables in the training dataset, the most influential variable was age, followed by sUA, BMI, CRP, and TG levels (Figure 4A).

Age exerted the most negative effect on IR prediction (Figure 4B). When plotted individually (Supplementary Figure S1), younger age was associated with inadequate response and older age was associated with response. Patients with a higher BMI and higher sUA, CRP, or TG levels were less likely to reach the serum urate goal, particularly for values above normal. Furthermore, the interaction analysis among the five variables showed that they contributed to the predictive model in a linear fashion (Supplementary Figure S2). For example, older age corresponded to a lower value of sUA (red dots), which interacted most with sUA.

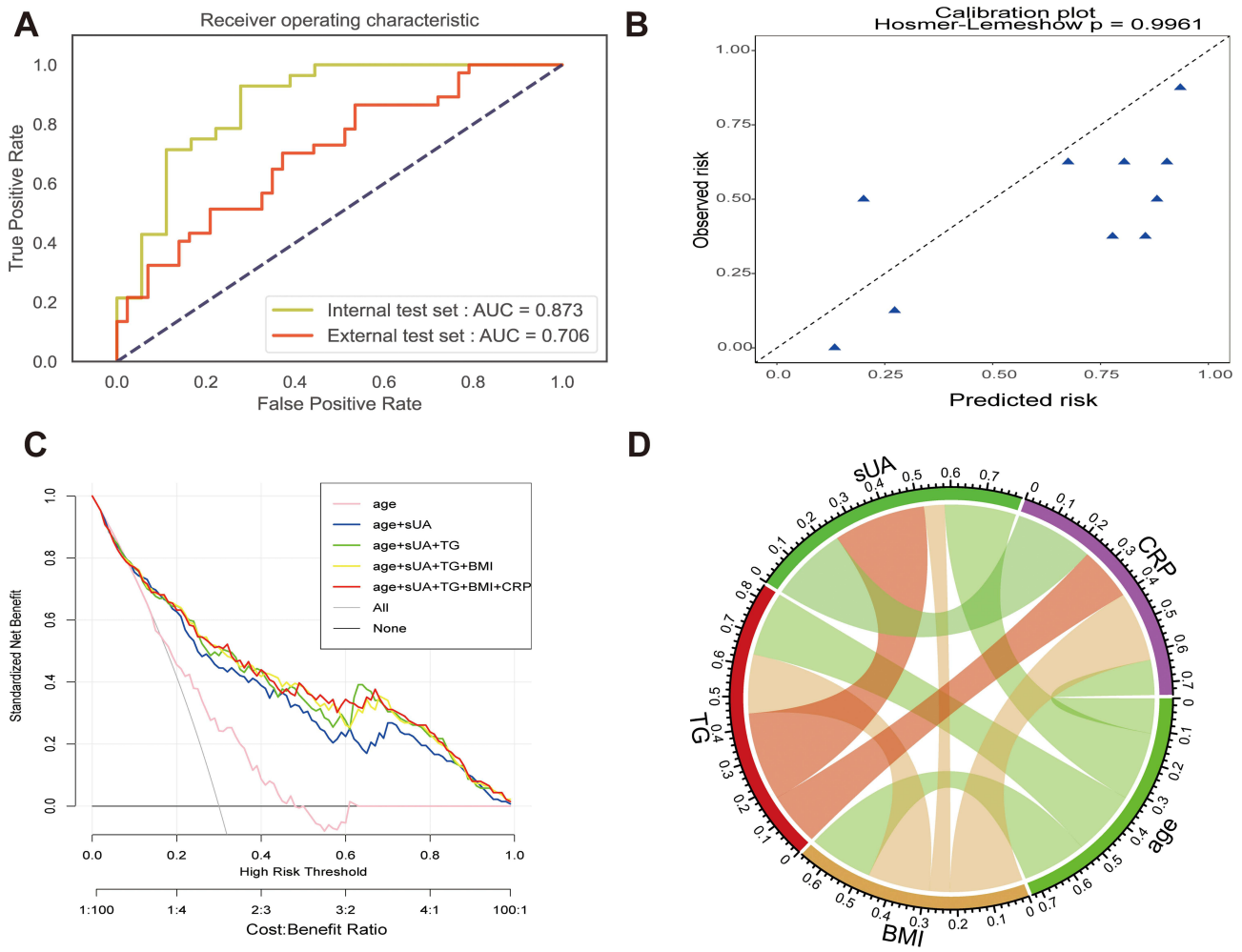

Figure 3 Model performance and evaluation. The area under the receiver-operator characteristic curve on the internal validation and external test sets of stochastic gradient descent (SGD) classifier (**A**), the calibration plot of the SGD model in the test set (**B**), the decision curve (**C**), and the correlation analysis between the features (**D**).
Abbreviation: AUC, the area under the receiver operating characteristic curve; sUA, serum urate; TG, triglyceride; BMI, body mass index; CRP, C-reactive protein.

Discussion

In the present study, we demonstrated that younger age, higher BMI, and higher baseline sUA, triglyceride, CRP levels were associated with failure to achieve the sUA target in patients with gout receiving low-dose febuxostat during the early ULT period. Based on machine learning algorithms using these variables, we could robustly predict inadequate responders to low-dose febuxostat. These findings may have clinical applicability, allowing for the identification of patients who are likely to require low-dose febuxostat treatment to achieve a serum urate target.

The promoted sUA target appeared realistic for almost half of the patients, followed by a low-dose strategy in both the short- and mid-term follow-up timeframes. Although a higher dose was recommended by the guidelines and the target rate was increased, the low dose was prone to be maintained in usual daily care. Moreover, excessive medication burden is linked to poor ULT adherence in patients with gout,[20] with consequent undertreatment.[21,22] It is likely that participants who respond to low-dose febuxostat will benefit from a personalized febuxostat dose regimen, allowing patients to receive the right dose without underdosing or using excessively high doses of medication.

It has been shown that age, BMI, sUA, TG, and CRP levels might be early predictors of which patients could benefit from low-dose febuxostat therapy. Inadequate responders were younger than responders, which is in line with the results of a real-world study.[23] One possible interpretation is that the included older patients may have received persistent ULT treatment for a period prior to enrollment. Additionally, younger age was a predictor of poor adherence to ULT. Low-dose febuxostat is more suitable for older patients with a high prevalence of comorbidities.[24] Baseline BMI and sUA

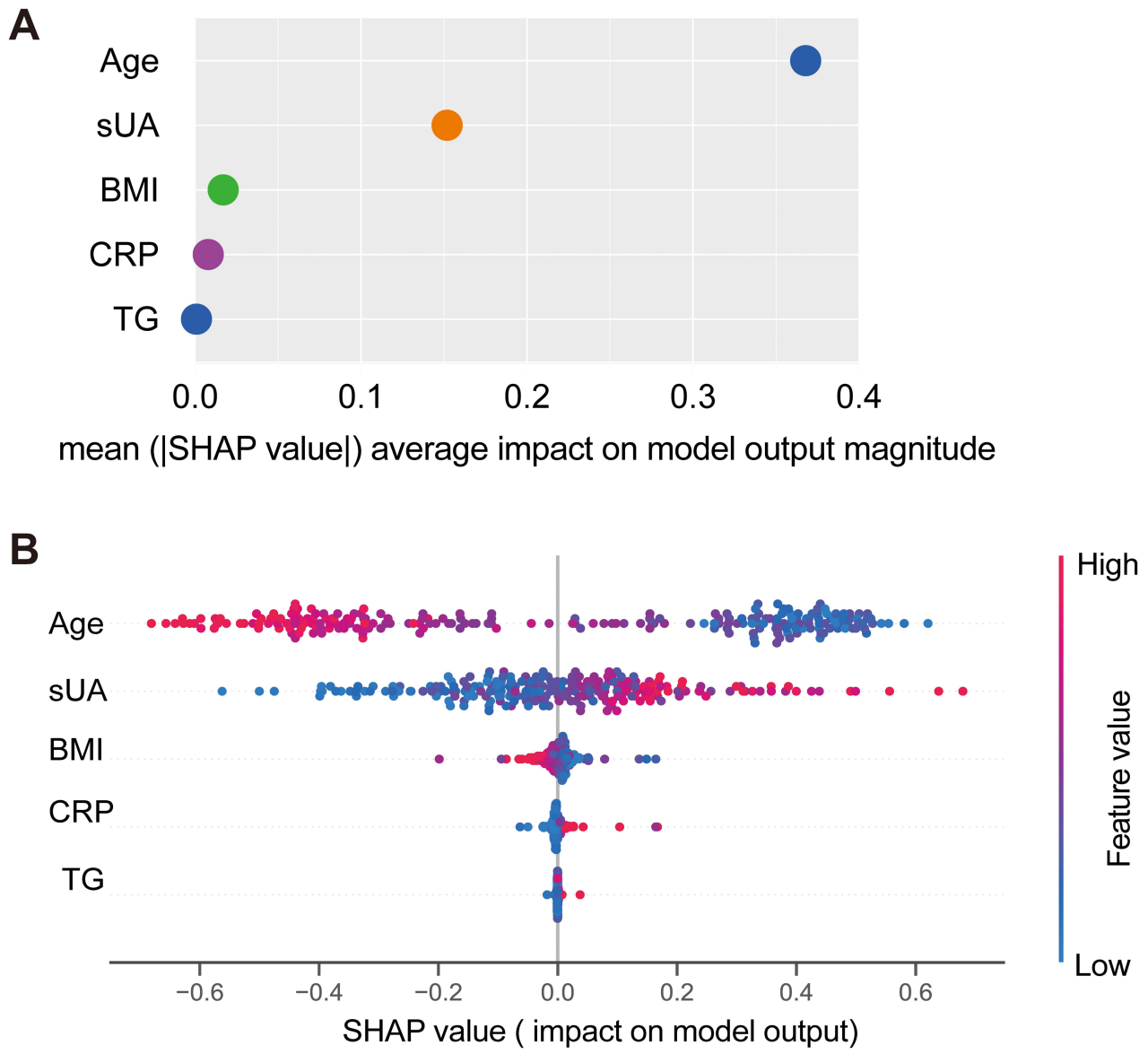

Figure 4 Febuxostat inadequate response interpreted by the trained stochastic gradient descent model with Shapley additive explanations (SHAP). The global importance of five features based on the average SHAP value magnitude (**A**). A set of bee-swarm plots corresponding to feature summary (**B**). The vertical axis shows the sorted five features while the horizontal axis displays the impact on the model output. Each data point represents a predicted output and the color indicates the feature values.
Abbreviation: sUA, serum urate; TG, triglyceride; BMI, body mass index; CRP, C-reactive protein; SHAP, Shapley Additive exPlanations.

levels have been consistently associated with ULT responses in clinical trials and real-world studies,[14,23,25] which is consistent with our results. A higher serum urate level reflects a higher total urate burden, thereby requiring a higher dose to achieve the target serum urate.[26]

Multivariate analysis and the present model highlight the potential role of TG as a predictor of febuxostat IR. The association between TG and gout has been well established, however, the effect of TG on patient responses to febuxostat has not been determined. It was recently reported that febuxostat could regulate free fatty acid and lipid metabolism,[27,28] indicating that hypertriglyceridemia may reflect the state of xanthine oxidase activity in the early phase of ULT. Notably, both BMI and TG levels were included in the model. It is possible that a high TG level could attenuate the urate-lowering effect of low-dose febuxostat or that a high TG level reflects more severe metabolic syndrome. Additionally, inflammatory status, as assessed by CRP levels, is a predictor of IR to low-dose febuxostat. The other imaging features and blood

parameters did not provide any additional information. Further studies are required to identify the underlying mechanisms, as well as to explore how these predictors perform in clinical settings.

The ML model in the present study demonstrated reliable prediction of IR to low-dose febuxostat in the development set, with satisfactory replication in an independent test cohort. This finding is consistent with the predictors selected in the univariate and multivariate analyses. This is the first assessment using the ML approach to predict IR to febuxostat, with an AUC comparable to that of other studies such as methotrexate.[29] Our model supports that patients were appropriate for febuxostat dose escalation with a confidence of 61.9% (PPV), whereas others tended to benefit from maintaining a low-dose regimen. This model has several potential benefits and can be aligned with the individualization of ULT titration recommended in the 2020 American College of Rheumatology gout management guidelines.[2] At present, guidelines recommend febuxostat dose up-titration at intervals of 2–4 weeks.[30] Such a prediction model allows the identification of patients who require more frequent blood test monitoring. Recently, Qi et al assessed the proportion of achieved the serum urate target among hyperuricemia subtypes in another cohort receiving dose-escalation febuxostat, concluding that combined subtype has a lower response to febuxostat, compared to those with either overload or underexcretion subtype.[31] Overall, combined subtype hyperuricemia (OR = 0.64, 95% CI 0.41–0.99, P = 0.048) and baseline serum urate (OR = 0.74, 95% CI 0.62–0.89, P = 0.001) were independently associated with lower rates of achieving SU target among six variables including age, disease duration, BMI, baseline serum urate, TG/HDL-C and subtypes. In Qi et al, the important finding was prescribing febuxostat according to hyperuricemia subtype, while it is available for clinicians to tailor individualized febuxostat treatment according to our findings.

The limitations of this study include patients with severe chronic kidney disease and low baseline serum urate levels being excluded from rigorous clinical trials, which limits the generalizability of the potential predictors. Additionally, a general limitation of this study is that the basic mechanism(s) of IR to febuxostat are not known. Although febuxostat inhibits the urate excretory transporter ABCG2 at clinically relevant concentrations,[32] previous studies have not shown that the ABCG2 genotype (rs2231142 allele) alters the febuxostat response.[33] Febuxostat can impede the access channel to the xanthine oxidase/dehydrogenase active site, and febuxostat disposition is primarily mediated by the activity of hepatic UDP-glucuronosyltransferase and Cytochrome P450 (CYP) enzymes.[34] Importantly, it is not yet known whether individualizing febuxostat doses according to selected predictors will improve clinical outcomes. Although the quality of evidence for the efficacy of low-dose febuxostat is relatively limited, the benefits of low-dose febuxostat may include fewer gout flares in the first few months after treatment initiation.[6]

In conclusion, participants who were administered low-dose febuxostat may respond according to baseline sUA but also TG, CRP, age, and BMI at the mid-term follow-up. These findings suggested a stratified treatment regimen for patients with gout. The robust ML prediction model for inadequate serum urate response may allow the identification of patients who are likely to require dose escalation of febuxostat to achieve the serum urate target.

Data Sharing Statement

The data used in this study are available upon agreement from the scientific committee for each cohort.

Ethics Approval and Consent to Participate

All participants provided written informed consent. The scientific committees of the Affiliated Hospital of Qingdao University of the three cohorts approved the use of data for this study. The study was conducted in accordance with the Declaration of Helsinki.

Acknowledgments

The authors acknowledge the scientific committee for approving the provision of all data for this study. They also thank all of the investigators who performed expert monitoring and data management, and recruited and followed the patients.

Funding

This study was sponsored by the Shandong Provincial Science Foundation for Youth Scholars (#ZR2023QH147), National Natural Science Foundation of China (#82220108015), National Key R&D Program of China

(#2022YFC2503300 and #2022YFE0107600), Taishan Scholar Program of Shandong Province (#tsqn202211377), and Shandong Provincial Science Foundation for Outstanding Youth Scholars (#ZR2021YQ56).

Disclosure

N.D. received consulting fees, speaker fees, or grants from AstraZeneca, Novartis, Dyve Biosciences, Horizon, Selecta, Arthrosi, JW Pharmaceutical Corporation, PK Med, LG Chem, JPI, PTC Therapeutics, Protalix, Cello Health, JPI, Dexoligo Therapeutics, Unlocked Labs, and Hikma outside the submitted work. R.T. reports personal fees from LG Chem, Atom Biosciences, Fortress, Astra-Zeneca, Generate, Synlogic, non-salaried President of the G-CAN (Gout, Hyperuricemia, and Crystal-Associated Disease Network) research society, which annually receives unrestricted arms-length grant support from pharma donors, during the conduct of the study. The authors report no other conflicts of interest in this work.

References

1. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheumatic Dis*. 2017;76(1):29–42. doi:10.1136/annrheumdis-2016-209707
2. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American college of rheumatology guideline for the management of gout. *Arthritis Care Res*. 2020;72(6):744–760.
3. Stamp LK, Dalbeth N. Critical appraisal of serum urate targets in the management of gout. *Nat Rev Rheumatol*. 2022;18(10):603–609. doi:10.1038/s41584-022-00816-1
4. Stamp LK, Chapman PT, Barclay ML, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. *Ann Rheum Dis*. 2017;76(9):1522–1528.
5. Doherty M, Jenkins W, Richardson H, et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. *Lancet*. 2018;392(10156):1403–1412.
6. Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353(23):2450–2461.
7. Ye P, Yang S, Zhang W, et al. Efficacy and tolerability of febuxostat in hyperuricemic patients with or without gout: a systematic review and meta-analysis. *Clin Ther*. 2013;35(2):180–189. doi:10.1016/j.clinthera.2012.12.011
8. Sheer R, Null KD, Szymanski KA, et al. Predictors of reaching a serum uric acid goal in patients with gout and treated with febuxostat. *Clinicoecon Outcomes Res*. 2017;9:629–639. doi:10.2147/CEOR.S139939
9. Graham GG, Stocker SL, Kannangara DRW, et al. Predicting response or non-response to urate-lowering therapy in patients with gout. *Curr Rheumatol Rep*. 2018;20(8):47. doi:10.1007/s11926-018-0760-2
10. Becker MA, MacDonald PA, Hunt BJ, et al. Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy. *Nucleo Nucle Nuc Acid*. 2008;27(6):585–591.
11. Yamanaka H, Tamaki S, Ide Y, et al. Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study. *Ann Rheum Dis*. 2018;77(2):270–276. doi:10.1136/annrheumdis-2017-211574
12. Dalbeth N, Stamp LK. Gout: why compare the effectiveness of suboptimal gout management? *Nat Rev Rheumatol*. 2015;11(9):506–507. doi:10.1038/nrrheum.2015.94
13. Kamatani N, Fujimori S, Hada T, et al. Placebo-controlled, double-blind study of the non-purine-selective xanthine oxidase inhibitor Febuxostat (TMX-67) in patients with hyperuricemia including those with gout in Japan: Phase 3 clinical study. *J Clin Rheumatol*. 2011;17(4 Suppl 2):S13–S18. doi:10.1097/RHU.0b013e31821d36cc
14. Liang N, Sun M, Sun R, et al. Baseline urate level and renal function predict outcomes of urate-lowering therapy using low doses of febuxostat and benzbromarone: a prospective, randomized controlled study in a Chinese primary gout cohort. *Arthritis Res Ther*. 2019;21(1):200.
15. Yan F, Xue X, Lu J, et al. Superiority of low-dose benzbromarone to low-dose febuxostat in a prospective, randomized comparative effectiveness trial in gout patients with renal uric acid underexcretion. *Arthritis Rheumatol*. 2022;74(12):2015–2023.
16. Bando Y, Toyama H, Kanehara H, et al. Chronic hyperglycemia may attenuate the serum-uric-acid-lowering effect of low-dose febuxostat in Japanese patients with type 2 diabetes mellitus. *Diabetol Int*. 2016;7(3):1.
17. Ichiro Hisatome KI, Mineo I. Japanese society of gout and uric & nucleic acids 2019 guidelines for management of hyperuricemia and Gout 3rd edition. *Gout and Uric Nucleic Acids*. 2020;44:1.
18. Singh JA, Akhras KS, Shiozawa A. Comparative effectiveness of urate lowering with febuxostat versus allopurinol in gout: analyses from large U.S. managed care cohort. *Arthritis Res Ther*. 2015;17(1):120.
19. Hu S, Sun M, Li M, et al. Elevated serum CA72-4 predicts gout flares during urate lowering therapy initiation: a prospective cohort study. *Rheumatology*. 2022.
20. Scheepers L, van Onna M, Stehouwer CDA, et al. Medication adherence among patients with gout: a systematic review and meta-analysis. *Semin Arthritis Rheum*. 2018;47(5):689–702. doi:10.1016/j.semarthrit.2017.09.007
21. Qaseem A, Harris RP, Forciea MA, et al. Management of acute and recurrent gout: a clinical practice guideline from the American college of physicians. *Ann Intern Med*. 2017;166(1):58–68.
22. Abhishek A, Doherty M. Education and non-pharmacological approaches for gout. *Rheumatology*. 2018;57(suppl_1):i51–i58.
23. Hatoum H, Khanna D, Lin SJ, et al. Achieving serum urate goal: a comparative effectiveness study between allopurinol and febuxostat. *Postgrad Med*. 2014;126(2):65–75. doi:10.3810/pgm.2014.03.2741

24. Kang EH. Considerations for choosing first-line urate-lowering treatment in older patients with comorbid conditions. *Drugs Aging*. 2022;39(12):923–933. doi:10.1007/s40266-022-00986-3
25. Stamp LK, Chapman PT, Barclay M, et al. Can we predict inadequate response to allopurinol dose escalation? Analysis of a randomised controlled trial. *Rheumatology*. 2018;57(12):2183–2189. doi:10.1093/rheumatology/key237
26. Graham GG, Kannangara DR, Stocker SL, et al. Understanding the dose-response relationship of allopurinol: predicting the optimal dosage. *Br J Clin Pharmacol*. 2013;76(6):932–938.
27. Heikal MM, Shaaban AA, Elkashef WF, et al. Effect of febuxostat on biochemical parameters of hyperlipidemia induced by a high-fat diet in rabbits. *Can J Physiol Pharmacol*. 2019;97(7):611–622. doi:10.1139/cjpp-2018-0731
28. Guma M, Dadpey B, Coras R, et al. Xanthine oxidase inhibitor urate-lowering therapy titration to target decreases serum free fatty acids in gout and suppresses lipolysis by adipocytes. *Arthritis Res Ther*. 2022;24(1):175. doi:10.1186/s13075-022-02852-4
29. Duquesne J, Bouget V, Cournede PH, et al. Machine learning identifies a profile of inadequate responder to methotrexate in rheumatoid arthritis. *Rheumatology*. 2022.
30. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American college of rheumatology guidelines for management of gout. part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res*. 2012;64(10):1.
31. Qi H, Sun M, Terkeltaub R, et al. Response to febuxostat according to clinical subtypes of hyperuricemia: a prospective cohort study in primary gout. *Arthritis Res Ther*. 2023;25(1):241.
32. Miyata H, Takada T, Toyoda Y, et al. Identification of febuxostat as a new strong ABCG2 inhibitor: potential applications and risks in clinical situations. *Front Pharmacol*. 2016;7(518). doi:10.3389/fphar.2016.00518.
33. Stamp LK, Topless R, Miner JN, et al. No association between ATP-binding cassette transporter G2 rs2231142 (Q141K) and urate-lowering response to febuxostat. *Rheumatology*. 2019;58(3):547–548.
34. Mukoyoshi M, Nishimura S, Hoshide S, et al. In vitro drug-drug interaction studies with febuxostat, a novel non-purine selective inhibitor of xanthine oxidase: plasma protein binding, identification of metabolic enzymes and cytochrome P450 inhibition. *Xenobiotica*. 2008;38(5):496–510. doi:10.1080/00498250801956350